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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

OFFICE OF CHEMICAL SAFETY AND POLLUTION PREVENTION

MEMORANDUM

Date: July 7, 2011

SUBJECT: EPTC: Revised/ Updated Developmental Neurotoxicity Toxicity Study in rats (MRID# 46319101)

PC Code: 041401
MRID No.: 46319101
Petition No.: NA
Assessment Type: Single Chem
TXR No.: 0056050

DP Barcode: D390210
Registration No.: 10163-283
Regulatory Action: Registration New use
Reregistration Case No.: NA
CAS No.: 759-94-4

FROM: Judy Facey, Ph.D., Toxicologist
Risk Assessment Branch VI
Health Effects Division (7509P)

Judy Facey 7/7/2011

TO: Bethany Benbow, Risk Management Team 25
Herbicide Branch
Registration Division (7505P)

THROUGH: Felecia Fort, Branch Chief
Risk Assessment Branch VI
Health Effects Division (7509P)

Felecia Fort 7/13/2011

I. CONCLUSIONS

The EPTC Data Evaluation Record for the Developmental Neurotoxicity study in rat (MRID# 46319101) was reviewed and a new supplemental Data Evaluation Record was created.

II. ACTIONS REQUESTED

HED completed a supplemental Data Evaluation Record for the acceptable Developmental Neurotoxicity study in rats (MRID#46319101).

Rec'd in RAC 7/19/2011 EL

III. RESULTS/DISCUSSION

The Developmental Neurotoxicity study in rats was reviewed and a supplemental Data Evaluation Record was created.

Study Type	MRID	Comments
EPTC Developmental Neurotoxicity study- Rats	46319101	Supplemental DER

EPA Reviewer: Judy Facey Ph.D **Signature:** Judy Facey
Registration Action Branch 6, Health Effects Division (7509P) **Date:** 7/7/2011
EPA Reviewer: Stephen Dapson Ph.D. **Signature:** Stephen C. Dapson
Registration Action Branch 6, Health Effects Division (7509P) **Date:** 07/07/2011

Template version 02/06

TXR#:0056050

SUPPLEMENTAL DATA EVALUATION RECORD TXR# 0052747

STUDY TYPE: Developmental Neurotoxicity Study - Rat; OPPTS 870.6300 (§83-6); OECD 426 (draft)

PC CODE: 041401 **DP BARCODE:** D390210

TEST MATERIAL (PURITY): EPTC (98.1% a.i.; Batch#: FL021317)

SYNONYMS: S-Ethyl-N, N-dipropylthiocarbamate

CITATION: Lees, D (2004) EPTC: Developmental neurotoxicity study in rats. Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK. Laboratory Project ID: CTL Study Number: RR0926, July 2, 2004. MRID 46319101. Unpublished

SPONSOR: Gowan Company, PO Box 5569, Yuma, AZ 85366.

EXECUTIVE SUMMARY:

In a developmental neurotoxicity study (MRID 46319101) EPTC (98.1% a.i.; Batch #: FL021317) was administered in the diet to pregnant Wistar rats (30/dose) from gestation day (GD) 7 to lactation day (LD) 23 at nominal doses of 0, 100, 300 or 1000 ppm (equivalent to 0/0. 7.6/16.4, 21.9/47.9, and 67.2/157.3 mg/kg/day [gestation/lactation]). Dams were allowed to deliver naturally and were killed on LD 29. On postnatal day (PND) 5, litters were standardized to 8 pups/litter; the remaining offspring and dams were sacrificed and discarded without further examinations. Subsequently, 1 pup/litter/group (at least 10 pups/sex/dose when available) were allocated to subsets for FOB, motor activity, acoustic startle response, learning and memory evaluation, and neuropathological examination. Positive control data were not submitted with this study; however, summaries of positive control data previously submitted to the Agency were obtained and reviewed.

The **maternal LOAEL** is 1000 ppm (67.2 mg/kg/day) based on clinical signs (piloerection, hunched posture, sides pinched in); decreased body weight, body weight gain, and food consumption; and increased incidence of whole litter losses. The **maternal NOAEL** is 300 ppm (21.9 mg/kg/day).

In the offspring, no treatment-related effects were noted in developmental landmarks. FOB (maternal or F_1), motor activity, auditory startle reflex habituation, learning and memory (watermaze), neuropathology, or brain morphology at any dose level. At the high dose (1000

ppm), the number of whole litter losses was significantly increased (6/28 treated vs 1/30 controls; Table 6a). When whole litter losses were included, the following differences were noted at 1000 ppm; (i) live birth index was slightly decreased (96.3 treated vs 99.7% controls); (ii) mean litter size (PND 5) was decreased ($p \leq 0.05$) by 19%; and (iii) survival (PND 1-5) was decreased ($p \leq 0.01$; 74% treated vs 91.9% controls). However, when whole litter losses were excluded live birth index, mean litter size, and survival (PND 1-5) were comparable to controls. Survival (PND 1-5; excluding whole litter losses) was decreased at 300 ppm (89.4% treated vs 95.1% control); however, this finding was not dose-dependent. On PND 1, increased incidences of pups considered to be cold (all treatment groups) and pups displaying hypothermia (1000 ppm). On PND I, pup body weights were decreases ($p < 0.01$) by 8-9% at 100 ppm group. Absolute brain weights of female pups were decreased (5%) on both PND 12 and 63 at the high dose only.

Marginal decrease in absolute (not relative) pup brain weight (4-6%) was observed in male pups on PND 63 at all dose levels. This marginal effect had no dose-response, was not seen after perfusion, and had no corresponding necrosis. Therefore this effect was considered marginal at best and not robust.

The **offspring LOAEL** is 1000 ppm (to 67.2 mg/kg/day; HDT) based on decreases in absolute brain weights in both male and female pups on PND 63. The **offspring NOAEL** is 300 ppm (21.9 mg/kg/day).

This study is classified **Acceptable** and may be used for regulatory purposes, however it does not satisfy the guideline requirement for a developmental neurotoxicity study in rats (OPPTS 870.6300. 83-6); OECD 426 (draft) at this time pending a comprehensive review of all available positive control data.

COMPLIANCE: Signed and dated Data Confidentiality. GLP Compliance, Flagging and Quality Assurance statements were provided.

Table 1a. Mean (±SD) absolute (g) and relative (to body, %) brain weights in F_1 male rats.[a]

Parameter	Dose (ppm)			
	0	100	300	1000
PND 12 (n= 9-13)				
Terminal Body Weight (g)	21.1 ± 2.8	22 ± 2.6	21.5 ± 1.4	21.3 ± 2.8
Absolute Brain Weight (g)	1.10 ± 0.05	1.13 ± 0.10	1.11 ± 0.04	1.07 ± 0.07
Relative (to body) Weight (%)	5.27 ± 0.56	5.19 ± 0.46	5.17 ± 0.32	5.08 ± 0.40
Adjusted for Body Weight (g)	1.11	1.12	1.11	1.08
PND 63 (n= 10-15)				
Terminal Body weight (g)	338.7 ± 16.6	334.5 ± 20.5	331.7 ± 24	326.9 ± 22.3
Absolute Brain Weight (g)	2.03 ± 0.06	1.94 ± 0.05**(↓4%)	1.94 ± 0.09** (↓4%)	1.90 ± 0.07** (↓6%)
Relative (to body) Weight (%)	0.60 ± 0.04	0.58 ± 0.03	0.59 ± 0.03	0.58 ± 0.02
Adjusted for Body Weight (g)	2.02	1.94**(↓4%)	1.94**(↓4%)	1.91**(↓5%)
PND 63 (post- perfusion, n= 10-13)				
Terminal Body Weight (g)	338.0 ± 22.4	344.5 ± 24.5	335.8 ± 19.5	328.0 ± 28.2
Absolute Brain Weight (g)	1.94 ± 0.10	1.93 ± 0.09	1.94 ± 0.08	1.88 ± 0.08
Relative (to body) Weight (%)	0.58 ± 0.03	0.56 ± 0.04	0.58 ± 0.04	0.58 ± 0.05
Adjusted for Body Weight (g)	1.94	1.92	1.95	1.89

a Data were obtained from Study report Tables 26 and 27, pages 165-167. Percent difference from control (calculated by reviewers) is presented parenthetically.

** Statistically different from controls at p≤0.01.

Table 1b. Mean (±SD) absolute (g) and relative (to body, %) brain weights in F_1 female rats.[a]

Parameter	Dose (ppm)			
	0	100	300	1000
PND 12 (n= 9-13)				
Terminal Body Weight (g)	20.9 ± 2.4	20.5 ± 3.2	21.7 ± 2.0	20.5 ± 3.2
Absolute Brain Weight (g)	1.10 ± 0.05	1.07 ± 0.06	1.08 ± 0.06	1.04 ± 0.05* (↓5%)
Relative (to body) Weight (%)	5.29 ± 0.43	5.30 ± 0.66	4.98 ± 0.30	5.16 ± 0.61
Adjusted for Body Weight (g)	1.10	1.07	1.07*(↓3)	1.05** (↓5)
PND 63 (n= 10-13)				
Terminal Body weight (g)	210 ± 14.4	211.5 ± 13.4	212.3 ± 11.3	202.4 ± 12.7
Absolute Brain Weight (g)	1.82 ± 0.05	1.83 ± 0.07	1.82 ± 0.04	1.76 ± 0.08* (↓5%)
Relative (to body) Weight (%)	0.87 ± 0.05	0.87 ± 0.04	0.86 ± 0.05	0.87 ± 0.06
Adjusted for Body Weight (g)	1.82	1.82	1.82	1.78
PND 63 (post- perfusion, n= 10-15)				
Terminal Body Weight (g)	213.4 ± 11.3	208.9 ± 18.2	209.5 ± 14.2	219.5 ± 22.3
Absolute Brain Weight (g)	1.79 ± 0.08	1.79 ± 0.08	1.80 ± 0.08	1.75 ± 0.09
Relative (to body) Weight (%)	0.84 ± 0.05	0.86 ± 0.08	0.86 ± 0.07	0.80 ± 0.10
Adjusted for Body Weight (g)	1.79	1.79	1.80	1.74

a Data were obtained from Study report Tables 26 and 27, pages 165-167. Percent difference from control (calculated by reviewers) is presented parenthetically.

* Statistically different from controls at p≤ 0.05.

** Statistically different from controls at p≤ 0.01.

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R193110

Chemical Name: Carbamothioic acid, dipropyl-, S-ethyl ester

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